REMARKS

Claims 1-34 were pending in the instant application. Claims 18-34 are withdrawn from consideration as drawn to a non-elected invention. Claims 18-34 (Group II) are related to claims 1-17 (Group I) as product and process of use. It is the Applicant's understanding that, once the pending product claims are found allowable, any non-elected process claims (Group II, claims 18-34) will be rejoined and examined if such process claims include all of the limitations of the elected product claims (MPEP §821.04).

Claim 1 has been canceled and claims 2, 4, 10-15, 18, 19, 27 and 31 have been amended. Accordingly, claims 1-34 will be pending after entry of the instant amendment. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application. Support for the claim amendments can be found throughout the claims and specification as originally filed. No new matter has been added.

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of: (a) the Examiner's assertion that claims 3-9 are only entitled to a priority date of November 26, 2006; (b) the previous rejection of claims 6-7 under 35 U.S.C. § 112, second paragraph; and (c) the previous rejection of claims 4, 5 and 9 under 35 U.S.C. § 102(e).

Rejection of Claims 3-17 under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 3-17 as failing to comply with the written description requirement. In particular, the Examiner maintains that "[a]lthough the specification adequately describes siRNA compounds targeted to cells expressing reporters GFP and RFP (see Examples 1-3), by fully setting forth their sequence and function, and by describing the materials and methods needed to measure their activity, adequate written description does not exist for the virtually unlimited number of other siRNA in the claimed genus that target any mutant allele from any species."

Applicants respectfully traverse this rejection and reiterate below the arguments set forth in the previous Response filed May 15, 2006.

The fundamental factual inquiry in a written description rejection is whether the claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim ***need not be described literally*** (i.e. using the same terms or in haec verba) in order for the disclosure to satisfy the written description requirement. MPEP 2163.02. Rather, the inquiry into whether the written description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

Moreover, the Federal Circuit in *Capon* has firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, ***its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science***." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter***. *Id.* at 1359 (emphasis added).

The Court further explained that "the written description may be satisfied 'if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.'" *Id.* (citing *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (emphasis added)). Accordingly, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358.

Applicants submit that based on the foregoing considerations and framework for written description, particularly as articulated by the Federal Circuit in *Capon*, the subject matter of the pending claims is fully described in accordance with 35 U.S.C. §112, first paragraph, by the present specification.

Claim 3, and claims 4-17 which depend therefrom, are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the ***sense strand comprises***

a sequence homologous to a region of a mutant allele encoding a gain-of-function mutant protein, said ***region comprising one or more point mutations***, and wherein the ***antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations***, such that the siRNA directs allele-specific cleavage of a mRNA encoded by the mutant allele.

The Examiner alleges that "the art does not provide a core structure or motif that would function in directing allele-specific cleavage of any mutant allele" and concludes that "one is left to empirically screen for siRNA compounds of the invention." Applicants respectfully submit that ***Applicants' specification,*** and not the art, ***provides the core structure*** of the presently claimed siRNAs that functions in directing allele-specific cleavage of any mutant allele. In particular, Applicants' specification teaches that the ***critical structural feature*** of the siRNAs of the invention is the ***presence in the antisense strand of a modified base positioned opposite a point mutation in a target mRNA*** encoded by a mutant allele. Given this ***core structural feature***, one of ordinary skill in the art is put in possession of a broad variety of siRNA compounds that direct allele-specific cleavage of an mRNA encoded by a mutant allele. The remaining structure, *i.e.*, sequence, of the siRNAs of the invention ***depends necessarily on the sequence of the particular target mRNA*** and, accordingly, ***cannot be shared*** by all the siRNAs of the invention.

The Examiner further alleges that the general guidelines provided in the specification for generating siRNAs "do not address the particulars of the siRNA design and selection process required for obtaining siRNAs against any mutant allele such that one of ordinary skill in the art reading the specification at the time of filing could envision any siRNA targeted to an vast number of mutant alleles responsible for gain-of-function diseases." Contrary to the Examiner's allegation, the specification provides extensive guidance for designing and selecting the sequences of siRNAs which can be used for allele-specific cleavage in the present invention.

For example, Applicants provide a plethora of explicit examples of diseases caused by dominant, gain-of-function gene mutations, including Alzheimer's disease, Huntington's disease, Parkinson's disease and ALS (***see, e.g., page 1, second paragraph; page 18, line 12 through page 19, line 21; and references 1 and 41-56 as listed at pages 30-35 of the specification, all of which are incorporated by reference***). One of ordinary skill in the art would recognize that the sequences of the mutant alleles responsible for these diseases were common knowledge in the art and easily obtainable at the time of filing the instant application.

Further, the specification provides detailed guidance for the process of designing siRNA molecules to target a particular mutant allele (see, for example, pages 8-16 and, in particular, pages 10-11):

> 1. Beginning with an AUG start codon, search for AA dinucleotide sequences; each AA and the 3' adjacent 16 or more nucleotides are potential siRNA targets. ***The siRNA should be specific for a target region that differs by at least one base pair between the wild type and mutant allele, e.g., a target region comprising the gain-of-function mutation. In cases where the gain-of-function mutation is associated with one or more other mutations in the same gene, the siRNA can be targeted to any of the mutations.*** In some cases, the siRNA is targeted to an allelic region that does not comprise a known mutation but does comprise an allelic variation of the wild-type (reference) sequence. The first strand should be complementary to this sequence, and the other strand is identical or substantially identical to the first strand. ***In one embodiment, the nucleic acid molecules are selected from a region of the target allele sequence beginning at least 50 to 100 nt downstream of the start codon, e.g., of the sequence of SOD1.*** Further, siRNAs with lower G/C content (35-55%) may be more active than those with G/C content higher than 55%. Thus in one embodiment, the invention includes nucleic acid molecules having 35-55% G/C content. In addition, the strands of the siRNA can be paired in such a way as to have a 3' overhang of 1 to 4, *e.g.*, 2, nucleotides. Thus in another embodiment, the nucleic acid molecules can have a 3} overhang of 2 nucleotides, such as TT. The overhanging nucleotides can be either RNA or DNA.
>
> 2. Using any method known in the art, compare the potential targets to the appropriate genome database (human, mouse, rat, etc.) and eliminate from consideration any target sequences with significant homology to other coding sequences. One such method for such sequence homology searches is known as Basic Local Alignment Search Tool (BLAST), which is available at the National Institutes of Health (NIH)/National Library of Medicine's (NLM's) National Center for Biotechnology Information (NCBI) website.
>
> 3. Select one or more sequences that meet your criteria for evaluation. Further general information about the design and use of siRNA may be found in "The siRNA User Guide," available at the Max Planck Institute for Biophysical Chemistry website.

The specification further provides detailed guidance for selecting the appropriate modified bases and the positions at which modified bases are placed in the siRNAs of the invention. For example, the specification teaches that

> [w]here the mutation results in the ***replacement of a base in the target mRNA with an adenine***, siRNAs modified with ***U(5Br) or U(5I) in the antisense strand***

are generally used. Where the mutation results in ***the replacement of a base target RNA with a uracil (thymine*** in the DNA), siRNAs modified with ***DAP in the antisense strand are generally used.*** (See pages 7-8, bridging paragraph).

Finally, Applicants' specification provides ample guidance for how to test and select siRNA molecules based on their ability to inhibit target mRNA expression, *e.g.*, in Examples 1-3 at pages 28-30 of the specification. Moreover, such techniques were routine in the art at the time of filing of the present application.

In view of the foregoing, it is evident that one of ordinary skill in the art would have recognized that, based on the teachings in the present specification, Applicants were in possession of the claimed invention at the time of filing.

Moreover, Applicants submit that, at the time the present application was filed, the existing knowledge in the siRNA field and the maturity of the RNAi technology was great. Indeed, it was common knowledge in the siRNA field how to go about selecting one or more specific target sequences in a target mRNA (*e.g.*, as described in detail by Applicants, as set forth above), how to generate one or more siRNA molecules targeted to that particular mRNA sequence and, moreover, how to test a panel of siRNA molecules for the ability to inhibit expression of the target mRNA. Such techniques were routine to one of ordinary skill in the art at the time the present application was filed. Further, the level of skill in the art with respect to incorporating modified nucleotides into RNA was similarly high at the time of filing the present application.

Accordingly, for at least the foregoing reasons, it would have been clear to one of ordinary skill in the art, based on the present specification and the high level of skill in the relevant art, that Applicants' had full possession of the claimed invention at the time of filing. Applicants therefore respectfully request the Examiner to reconsider and withdraw this rejection under 35 U.S.C. §112, first paragraph.

Rejection of Claims 1-2, 4-5 and 10-17 Under 35 USC § 102(e)

The Examiner has maintained the rejection of claims 1-2, 4-5 and 10-17 as being anticipated by Tuschl *et al.* (WO 02/44321). The Examiner alleges that "Tuschl et al. teach a

siRNA comprising at least one modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil that are *capable*, absent evidence to the contrary, of enhancing single nucleotide discrimination or enhancing binding interactions between the siRNA and mRNA." The Examiner concludes, based on the foregoing, that "Tuschl et al. anticipates claims 1-2, 4-5 and 10-17."

Claim 1 has been canceled, thereby rendering the rejection moot as it pertains to this claim. With respect to claim 2 and the claims which depend therefrom, Applicants respectfully traverse this rejection on the grounds that the cited reference fails to teach each and every element of the present invention as recited in the claims.

Claim 2, as currently amended, is drawn to a small interfering RNA (siRNA) ***capable of single nucleotide discrimination between a first and second allele***, the first allele having 1, 2, 3 or more point mutations relative to the second allele, wherein the siRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a modified base ***positioned opposite at least one point mutation in the first allele***, and wherein the modified base is ***capable of enhancing binding interactions between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele***. Claims 4-5 and 10-17 depend from claim 2.

For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach **each and every element** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

The claimed invention is directed to siRNAs having a particular structure, *i.e.*, siRNAs comprising an antisense strand that comprises ***a modified base positioned opposite at least one point mutation in a first allele***, and a specific function imparted by the structure, *i.e.*, the modified base is ***capable of enhancing binding interactions*** between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele, and a particular function, such that the siRNAs are ***useful for single nucleotide discrimination between a first and second allele***. The specification teaches and, indeed, the claimed invention is based, at least in part, on the biochemical principle underlying why such a structure mediates the function of single nucleotide discrimination.

Tuschl *et al.* is generally directed to siRNA molecules useful for mediating RNA interference. Tuschl *et al.* disclose that the ***stability of siRNAs against degradation*** may be

enhanced by the "substitution of pyrimidine nucleotides by modified analogues" (see page 5, first paragraph). Tuschl *et al.* disclose that these modified pyrimidine analogues may be nucleobase-modified ribonucleotides, including "uridines or cytidines modified at the 5-position, *e.g.*, ... 5-bromo uridine" (see page 5, third paragraph). Tuschl *et al.* fail to teach both the structure and the function imparted by that structure of the presently claimed siRNAs. In particular, Tuschl *et al.* fail to teach or suggest the specific ***positioning*** of a modified base in the ***antisense strand*** of an siRNA ***opposite a point mutation in the target mRNA*** of a mutant allele. Further, Tuschl *et al.* fail to teach or suggest that nucleobase-modified ribonucleotides ***at any position*** in an siRNA, let alone at the position required by the pending claims, are useful for enhancing binding interactions between the siRNA and an mRNA encoded by a first allele as compared to a second allele, when the first allele has 1, 2, 3 or more point mutations relative to the second allele. Indeed, Tuschl *et al.* fail to teach or suggest an siRNA comprising a modified base for any purpose other than to increase stability. Thus the teachings of Tuschl *et al.* fail to anticipate the instant claims.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1, 4-5 and 10-17 under 35 § 102(e) be reconsidered and withdrawn.

Rejection of Claim 3 Under 35 USC § 102(e)

The Examiner has maintained the rejection of claim 3 as being anticipated by Xu *et al.* (US 2004/0192629). The Examiner alleges that Xu *et al.* teach "a siRNA comprising a modified base position[ed] opposite a point mutation of the sod1 gene (***see Figure 1A***)" (emphasis added) and concludes that Xu *et al.* "is available as a reference under 102(e) and anticipates claim 3 of the instant application."

Applicants respectfully reiterate that Xu *et al.* is not available as a 102(e) reference against the instant invention with regard to the disclosure of an siRNA comprising a modified base. As set forth in the previous Response filed May 15, 2006, claim 3 is entitled to a priority date of March 26, 2003. Further, the Xu *et al.* application claims priority to two U.S. patent applications, only one of which has a filing date preceding the priority date of the instant claims (US Application No. 60/423,507, filed November 4, 2002). Contrary to the Examiner's assertion, the Xu *et al.* priority document 60/423,507 does not teach an siRNA comprising a ***modified base*** positioned opposite a point mutation of the sod1 gene. The Xu *et al.* priority

document discloses in Figure 1A a sod1 mutant mRNA sequence comprising a point mutation G to C (substitution of guanine with cytosine) relative to the sod1 wild type mRNA sequence (see Figure 1A). Figure 1A of the Xu *et al.* priority document further discloses siRNAs targeting the wild type and mutant sod1 mRNAs, wherein the antisense strands of the siRNAs comprise ***standard nucleotides*** and have sequences perfectly complementary to their respective target mRNA sequences. In particular, the Xu *et al.* priority document depicts in Figure 1A siRNAs targeted to the mutant sod1 mRNA, wherein the antisense strand has a ***guanine*** positioned opposite the point mutation, i.e., cytosine, in the mutant mRNA sequence, and further depicts siRNAs targeted to the wild type sod1 mRNA, wherein the antisense strand comprises a cytosine positioned opposite the guanine located at the site corresponding to the point mutation. Thus, the Xu *et al.* priority document teaches in Figure 1A the substitution of cytosine with ***guanine*** in the siRNA antisense strand in order to selectively target the mutant *sod1* mRNA.

Applicants respectfully submit that the nucleotide guanine is a standard, naturally-occurring nucleotide and is ***not a modified nucleotide or modified base***. Applicants' specification defines a "modified base" or "modified nucleotide" as follows:

> The term "nucleotide analog", also referred to herein as an "altered nucleotide" or ***"modified nucleotide" refers to a non-standard nucleotide***, including ***non-naturally occurring*** ribonucleotides or deoxyribonucleotides. Preferred nucleotide analogs are modified at any position so as to alter certain chemical properties of the nucleotide yet retain the ability of the nucleotide analog to perform its intended function. (See page 4, lines 24-28).

The present application teaches that "[s]uch ***modified nucleobases can be modified pyrimidines and/or purines, e.g., modified uracil, cytosine, adenine or guanine***" (see page 9, lines 13-15) and provides a plethora of exemplary modified nucleobases useful in the invention:

> In one embodiment, nucleobase-modified nucleotides useful in the invention comprise a modified pyrimidine, including, but not limited to: ribo-thymidine, 4-thio-uridine, 3-methyl-uridine, 5-bromo-uridine, 5-iodo-uridine, 5-fluoro-uridine, 5-amino-allyl-uridine (*e.g.*, 5-amino-methyl-uridine, 5-amino-ethyl-uridine, 5-amino-propyl-uridine, 5-amino-isopropyl uridine, and the like), 5,6-dihydro-uridine, 3-methyl-cytidine, 5-bromo-cytidine, 5-iodo-cytidine, 5-fluoro-cytidine, 5-amino-allyl-cytidine (*e.g.*, 5-amino-methyl-cytidine, 5- amino-ethyl-cytidine, 5-amino-propyl-cytidine, 5- amino-isopropyl-cytidine, and the like) and 5,6-

dihydro-cytidine. Nucleobase-modified nucleotides comprising a modified pyrimidine preferably are 5-bromo-uridine or 5-iodo-uridine.

In another embodiment, nucleobase-modified nucleotides useful in the invention comprise a modified purine, including, but not limited to: 6-thio-guanosine, 2-amino-purine (*e.g.*, 2-amino-adenosine), 2-amino-allyl-purine (*e.g.*, 2-amino-methyl-guanosine, 2-amino-dimethyl-guanosine, 2-amino-ethyl-guanosine, 2-amino-propyl-guanosine, 2-amino-isopropyl-guanosine, 2-amino-methyl-adenosine, 2-amino-dimethyl-adenosine, 2-amino-ethyl-adenosine, 2-amino-propyl-adenosine, and 2-amino-isopropyl-adenosine), 6-amino-purine (*e.g.*, 6-amino-guanosine), 6-amino-allyl-purine (*e.g.*, 6-amino-methyl-adenosine, 6-amino-dimethyl-adenosine, 6-amino-ethyl-adenosine, 6-amino-propyl-adenosine, and 6-amino-isopropyl-adenosine, 6-amino-methyl-guanosine, 6-amino-dimethyl-guanosine, 6-amino-ethyl-guanosine, 6-amino-propyl-guanosine, 6-amino-isopropyl-guanosine) and 2,6-diaminopurine. Nucleobase-modified nucleotides comprising a modified purine are preferably 2,6-diaminopurine. In yet another embodiment, nucleobase-modified nucleotides useful in the invention can comprise a purine modified at two positions, *e.g.*, 6-amino-2-bromo-purine, 6-amino-2-iodo-purine, 6-amino-2-fluoro-purine, 6-amino-8-bromo-purine, 6-amino-8-iodo-purine, 6-amino-8-fluoro-purine, 6-iodo-8-amino-purine, 6-bromo-8-amino-purine, 6-fluoro-8-amino-purine, and the like. A nucleobase-modified nucleotide comprising a purine modified at two positions is preferably 6-amino-8-bromo-purine. (See page 9, line 19 through page 10, line 13)

In view of the foregoing, it is evident that the Xu *et al.* priority document 60/423,507 fails to teach, e.g., in Figure 1A, an siRNA comprising a ***modified base*** positioned opposite a point mutation in a mutant allele, as required by pending claim 3. Accordingly, the Xu *et al.* disclosure of an siRNA containing a modified base can only be entitled to a filing date of the second priority application, *i.e.*, July 18, 2003, which is well after the priority date of the instant claims. Applicants therefore submit that the rejection of claim 3 under 35 U.S.C. § 102(e) as anticipated by Xu *et al.* is improper and respectfully request that it be reconsidered and withdrawn.

Rejection of Claims 3-5, 7 and 9 under 35 USC § 103(a)

The Examiner has maintained the rejection of claims 3-5, 7 and 9 under 35 U.S.C. §103(a) as being obvious over Xu *et al.* (US 2004/0192629) in view of Buhr *et al.* (US 6,476,205). The Examiner alleges that Xu *et al.* teach "a siRNA comprising a modified base

position[ed] opposite a point mutation of the sod1 gene (see Figure 1A)." The Examiner acknowledges that Xu *et al.* is not relied upon to teach modified bases comprising a 2,6-diaminopurine. The Examiner further relies on Buhr *et al.* for allegedly teaching that "it would be obvious to incorporate a modification such as a 1,6-diaminopurine into an siRNA."

Applicants maintain that Xu *et al.* is not available as a 103 reference against claims 3-5, 7 and 9 with regard to the disclosure of an siRNA comprising a modified base for the same reasons discussed above regarding the novelty rejection in view of Xu *et al.* As discussed above, claims 3-5, 7 and 9 are entitled to a priority date of March 26, 2003. Also as set forth above, the Xu *et al.* disclosure of an siRNA containing a modified base can only be entitled to a filing date of the second priority application, *i.e.*, July 18, 2003, which is well after the priority date of the instant claims. Applicants therefore submit that the rejection of claims 3-5, 7 and 9 under § 103(a) as being obvious over Xu *et al.* in view of Buhr *et al.* is improper and respectfully request that it be reconsidered and withdrawn.

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

By_____

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